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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,936	06/24/2003	Charles Jack Fisher	X12448B	1851

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ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,936	FISHER ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Preliminary Amendment filed 6/24/04 has been entered. Claims 1-20 have been cancelled and Claims 21-36 have been added. Claims 21-36 have been considered in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-25, 27, 30-33, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Claims 21-36 were added to the application by preliminary amendment and are not considered part of the original specification as filed. Claims 22, 25, 27, 30, 33 and 35 are limited to dose ranges that are not supported by the specification as originally filed. The specification does not teach the specific dosages of 6 µg/kg/hr to 36 µg/kg/hr (clms 22, 30) or administering protein C by continuous infusion specifically for about 48 hours to about 240 hours (clms 25, 27, 33, and 35). Claims 23, 24, 31, and 32 are rejected since they depend from independent claims that contain limitations not

supported by the original disclosure. Therefore, the claims contain subject matter that was not described in the specification in such a way as to reasonably convey that, at the time the application was filed, the inventors had possession of the claimed invention.

Claims 26-28 and 34-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 26 and 34 require that administration of recombinant human activated protein C achieve a recombinant human activated protein C plasma level of about 2 ng/ml to about 200 ng/ml. However, the specification does not teach how one would differentiate between recombinant protein C administered and protein C found naturally in the plasma. Thus, one of skill in the art would not know how to measure specifically the recombinant protein C in the plasma after administration of recombinant protein C. This rejection could be overcome by deleting "recombinant" in line 5 of Claims 26 and 34. Claims 27-28 and 35-36 are rejected because they depend from the rejected base claims yet do not correct their deficiencies.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab. Clin. Med. (1986) 108: 415-422; ref. CI of IDS filed 6/24/03) and Gruber et al. (Circulation (1990) 82: 578-585; ref. CH of IDS filed 6/24/03) and Foster et al. (U.S. Patent No. 5,516,650; ref. AB of IDS filed 6/24/03).

Glas-Greenwalt et al. teach the characteristics of TTP disorder in terms of blood biochemistry and physiology with respect to plasma fibrinolysis and protein C (PC). The reference teaches that PC levels are low in four out of 6 patients with TTP and that PC levels became normal after plasma exchange (Table II). The reference also teaches that it is possible that a defect in the fibrin-clearing system permits thrombus formation to occur and proceed in an unchallenged fashion thereby contributing to the complex events leading to arterial ischemia in vital organs.

Glas-Greenwalt et al. does not teach recombinant human protein C or its use in treating TTP.

Gruber et al. teach the inhibition of thrombus formation which is very similar to conditions of TTP (a platelet dependent thrombosis) by activated recombinant human protein C in a primate model of arterial thrombosis. The reference teaches methods of administering recombinant protein C wherein one third of the protein C is administered as a bolus and the remaining two thirds are given by continuous infusion (p. 579, Col. 1, last paragraph). Gruber et al. teach that recombinant human activated protein C, like the human plasma derived PC or plasma-derived activated protein C, inhibited thrombus formation. The reference teaches that the dosages used in the experiment significantly inhibited fibrin deposition in the graft and that circulating plasma markers of thrombus formation and fibrinolysis did not increase significantly during the infusion and that measurements of bleeding time were also within normal limits. While the dosages used in Gruber et al. are not the same as those of the claim, it was well within the skill of the ordinary artisan at the time of the invention to take the results from a method of treatment using a primate model and adjust the dosages such that they would apply to humans. Moreover, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (as cited in MPEP 2144.05 II).

Foster et al. teaches recombinant production of protein C. The reference teaches that while PC may be purified from clotting factor concentrates or from plasma

and activated in vitro, it is a complex and expensive process, in part due to the limited availability of the starting material and low concentration of PC in plasma. Furthermore, the therapeutic use of products derived from human blood carries the risk of disease transmission by viruses. The references teaches that it is preferable to use recombinant and activated recombinant PC and provides methods of producing recombinant PC.

Therefore, upon review of all three references as a whole, it appears that TTP (as well as HUS) are conditions that arise due to the formation of thrombi in peripheral arterioles leading to widespread occlusion of blood vessels. Gruber et al. teaches that recombinant protein C can be used successfully to treat platelet dependent thrombus formation in a model of arterial thrombosis. TTP is characterized by widespread arterial thrombosis wherein the microthrombi are rich in platelets and Glas-Greenwalt et al. teaches that patients with TTP have a protein C deficiency which can be normalized by plasma exchange. Therefore, it would have been obvious to one or ordinary skill in the art at the time of the invention, to combine the teachings of Glas-Greenwalt et al. with that of Gruber et al. and Foster et al. to develop a method of treatment for TTP using recombinant human PC. Gruber et al. and Foster et al teach that one would be motivated to do this in order to develop and use PC as an antithrombotic agent to treat septic shock and stroke which are final manifestations of TTP. The highly encouraging teachings of Gruber et al. using an arterial thrombosis model would have motivated one of ordinary skill in the art to extend the same to humans with the appropriate dosage and infusion methods. One of ordinary skill in the art would also be motivated to

develop and use a recombinant PC to avoid problems with the short supply of plasma and avoid contamination of the final product with potential pathogens. One of ordinary skill in the art would have had a reasonable expectation of success since Glas-Greenwalt et al. teach that PC antigen levels were low in TTP patients and that plasma (containing PC) exchange therapy resulted in temporary reversal of TTP abnormalities and Gruber et al. teach that recombinant activated PC inhibited thrombus formation in a model of arterial thrombosis.

Claims 29-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al., Gruber et al., and Foster et al. as applied to claims 21-28 above, and further in view of Hollenbeck et al. (Nephrol. Dial. Transplant. (1998) 13: 76-81; ref. CF in IDS filed 6/24/03).

The teachings of Glas-Greenwalt et al., Gruber et al., and Foster et al. have been described above.

However, Glas-Greenwalt et al., Gruber et al., and Foster et al. do not teach a method of using protein C to treat hemolytic uremic syndrome (HUS).

Hollenbeck et al. teach that both TTP and HUS are characterized by similar outcomes such as microangiopathic hemolytic anemia, thrombocytopenia, and functional impairment of various organs and that there is considerable overlap between the clinical pictures and morphological findings of both disorders such that the two disorders are now increasingly referred to HUS-TTP. Hollenbeck et al. also teaches that case reports and more recent prospective studies indicate that prognosis is

favorably influenced by plasma exchange. It is also well known in the art that plasma is a source of protein C and activated protein C.

Therefore, in view of the combined references of Glas-Greenwalt et al., Gruber et al., Foster et al.,and Hollenbeck et al., it would have been obvious to one of ordinary skill in the art to develop a method of treating HUS using recombinant protein C and recombinant activated protein C. While Hollenbeck et al. does not provide the dosages or steps of the method, given the close relationship between HUS and TTP and success in using protein C to treat thrombus formation disclosed in Gruber et al., it would have been well within the skill of the art to empirically set up dosages and safe methods of infusion for treatment of HUS. Moreover, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (as cited in MPEP 2144.05 II). One of ordinary skill in the art would have been motivated to do so in order to treat two closely related abnormalities such as TTP and HUS with a single agent. One of ordinary skill in the art would have had a reasonable expectation of success since Gruber et al. show promising results in using recombinant protein C to treat thrombus formation in an arterial thrombosis model.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-

0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
November 10, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER